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Effects of Inhalable Particles on Respiratory Health of Children[1-4]

DOUGLAS W. DOCKERY, FRANK E. SPEIZER, DANIEL O. STRAM, JAMES H. WARE, JOHN D. SPENGLER, and BENJAMIN G. FERRIS, JR.

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Introduction

A recent report (1) from the Six Cities Study of Air Pollution and Health described a strong association between frequencies of chronic cough, bronchitis, and chest illness in preadolescent schoolchildren and concentrations of particulate and sulfur oxide air pollution in six communities in the eastern United States. Illness and symptom rates were higher by approximately a factor of two in the community with the highest air pollution concentrations compared with the community with the lowest concentrations. No association was found, however, between air pollution concentrations and two measures of pulmonary function, FVC and FEV_1. Because the health data were gathered between 1974 and 1980, only three pollutant variables, total suspended particulates (TSP), the sulfate fraction of TSP (TSO_4), and sulfur dioxide concentrations (SO_2), were consistently available for this analysis. These measurements were gathered from stations operated by a variety of public and private agencies. Analysis of limited data on spatial and temporal variability of air pollution concentrations and respiratory health within the six cities found an association between total sulfate (TSO_4) concentrations and respiratory illness and symptom rates, but not with TSP or SO_2.

These results raised several issues requiring further investigation. (*1*) To what extent could these results be replicated using air pollution measurements gathered under standardized procedures established as part of the Six Cities Study? (*2*) Was the respiratory health status of study children associated with either of two measures of size-fractionated particulate matter, aerodynamic diameter less than 15 μm (PM_{15}) and less than 2.5 μm ($PM_{2.5}$)? Did ozone (O_3) or nitrogen dioxide (NO_2) concentrations have a direct effect on respiratory health or modify the associations with other pollutants? (*3*) Could associations be found between air pollution concentrations and potentially more sensitive measures of small airways impairment ($FEV_{0.75}$ and MMEF) obtained from digitized analysis of the spirometric tracings? (*4*) Could sensitive subgroups of the study population be identified?

This study investigated each of these issues by analyzing the respiratory health of the original cohort of the school children reexamined during the 1980–1981 school year, a period during which all elements of the study's air pollution measurement program, including size-fractionated particle measurements, were available in all six cities.

Methods

Populations Studied and Survey Procedures

The cohort of school children has been described elsewhere (1–3). Briefly, the children were initially seen as first- and second-graders attending schools in study communities during the enrollment period between 1974 and 1979. Each child had had an annual follow-up examination consisting of a respiratory symptom questionnaire completed by a parent and a spirometric examination performed at school. Health data used in this report were collected during the 1980–1981 school year. Three cities were visited between September and December, 1980: Watertown, MA; St. Louis, MO; and Portage, WI. And three were visited between January and April, 1981: Kingston-Harriman, TN; Steubenville, OH; and Topeka, KS.

Five respiratory illness and symptom responses obtained from the questionnaire were considered: bronchitis, cough, chest illness,

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[3] This report has not been subjected to the Environmental Protection Agency's required peer and policy review and therefore does not necessarily reflect the views of the Agency, and no official endorsement should be inferred.

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wheeze, and asthma (4). Bronchitis required a doctor's diagnosis in the last year; chronic cough was defined as being present for 3 months in the last year; chest illness required restriction of activities of 3 days or more. Persistent wheeze was defined as wheeze apart from colds or for most days or nights in the last year. Asthma required the reporting of a doctor's diagnosis.

Three symptoms not expected to be related to air pollution were also considered: earache, hay fever, and nonrespiratory illness or trauma that restricted activities for 3 days or more.

The spirometric examination has been described elsewhere (5). Briefly, the examination was performed using a water-filled recording spirometer (Survey Spirometer; Warren E. Collins, Braintree, MA) with the child in a sitting position without a noseclip. Each tracing was examined in the school by the local study coordinator. Those judged acceptable by standard criteria (4) were digitized centrally (6). The three best tracings varying by less than 150 ml were averaged to calculate the FEV_1, $FEV_{0.75}$, and FVC, and the tracing with the highest sum of FEV, and FVC was used to calculate the maximal midexpiratory flow (MMEF). All values were corrected to body temperature and pressure saturated with water (BTPS). The child's height and weight were measured in stockinged feet and recorded to the nearest centimeter and pound.

Air Pollution Measurements

A centrally located air monitoring station was established in each community at the time of the first health examination. SO_2, NO_2, O_3, and meteorologic variables were measured continuously. Integrated 24-h TSP samples were collected on a regular schedule. TSP samples were mailed to a central laboratory for determination of total mass concentration. Each site was audited semiannually by an independent agency using National Bureau of Standards traceable reference standards (7).

Beginning in 1978, dichotomous aerosol samplers were installed at each study site (8). The inlet of these samplers removes the larger particles (50% cut-size at 15 μm aerodynamic diameter). The aerosol is then divided into two fractions: the fine fraction with aerodynamic diameter less than 2.5 μm, and the coarse fraction between 2.5 and 15 μm. The two fractions were analyzed for mass concentration by beta-ray attenuation (9) and for elemental concentration by x-ray fluorescence (10). PM_{15} is the sum of the fine and coarse fractions. All elemental sulfur has been assumed to be present as sulfate ion (SO_4). All dichotomous samplers were operational for at least 1 yr prior to the 1980–1981 school year.

Daily mean concentrations of SO_2, NO_2, and O_3 were obtained by averaging hourly concentrations for each day with at least 18 hourly values. Three measures of particle mass ($PM_{2.5}$, PM_{15}, and TSP) were considered, as well as the concentration of elemental sulfate in the fine fraction, denoted here as FSO_4. Monthly means were calculated for each pollutant by averaging all available daily values. An air pollution exposure in the previous year was calculated for each child by averaging the monthly means for the 12 months preceding the month of the spirometric examination.

Statistical Methods

Previously reported analyses of illness and symptom rates and of pulmonary function levels established that city-to-city variation in health outcomes was larger than would be expected given interindividual variation in health outcomes (1). To account for this variability, we used two-step methods to analyze the health outcomes. In the analysis of illness and symptom rates, an initial logistic regression was used to estimate the adjusted logit of illness frequency in each of the six cities, controlling for sex, age, maternal smoking, and the presence of a gas stove in the home. In the second step, these estimated logits were regressed against the city-specific air pollution measurements using weights that were inversely proportional to the sum of the between-city variance and the within-city variance of the adjusted logits. The results of this regression are summarized here by the estimated relative odds of the illness or symptom rate in the most polluted and least polluted city. Ninety-five percent confidence intervals (95% CI) for these relative odds were calculated using Miettinen's test-based approximation (11).

For the pulmonary function measures, the same general scheme was used. In the first step, the logarithms of individual pulmonary function measurements were fitted to a linear function of the logarithm of height, age, maternal smoking, indicators for sex, parental education, gas cooking, and an interaction between sex and logarithm of height. In the second step, the adjusted city-specific means of the logarithms of pulmonary function measures were regressed on the air pollution variables. Each pollution variable was considered separately. The regression results are summarized by the estimated percentage difference in pulmonary function level between the most polluted and least polluted cities. This difference is given by the antilogarithm of the regression coefficient times the difference in pollutant concentrations. Ninety-five percent confidence intervals were calculated in the logarithmic scale, again using a test-based approximation.

TABLE 1

CITY-SPECIFIC AGE DISTRIBUTION OF WHITE CHILDREN IN COHORT

	10 yr	11 yr	12 yr	Total
Portage, WI	285	282	245	812
Topeka, KS	252	593	368	1,213
Watertown, MA	240	277	260	777
Kingston, TN	106	198	227	531
St. Louis, MO	283	363	350	996
Steubenville, OH	377	357	359	1,093
Total	1,543	2,070	1,809	5,422

A potentially sensitive subset of the population was defined by the presence of reported asthma or persistent wheeze. The two-step analysis was repeated to produce separate estimates of the air pollution associations in children with and without asthma or wheeze. In the first step, city-specific rates of respiratory symptoms were calculated for each group, after adjusting for the associations with sex, age, parental education, maternal smoking and gas stoves in the combined sample. In the second step, the city-specific adjusted rates were regressed on air pollution, separately for children with and without asthma or wheeze. An analogous procedure was used for analysis of pulmonary function measurements.

Results

A total of 8,131 children were seen during the 1980–1981 school year. Because the enrollment period varied among cities, the age distributions of these children also varied among cities. To avoid confounding caused by age and race, the analysis was restricted to the 5,422 10- to 12-yr-old white children examined in the 1980–1981 school year (table 1).

Adjustment for Covariates

Each symptom was analyzed using a logistic regression model including sex, age, indicators of parental education, maternal smoking (cigarettes per day), an indicator for gas stove, and an indicator for each of the cities. **Maternal smoking was significantly associated with most symptoms** (table 2). The coefficients for the respiratory symptoms investigated in the earlier report (bronchitis, chronic cough, chest illness, and persistent wheeze) were consistent with values obtained from analysis of the earlier examination (2). Asthma rates were not significantly associated with maternal smoking. **Of the referent symptoms, earache was significantly associated with maternal smoking,** whereas nonrespiratory illness and hay fever were not. As in the earlier examinations of these children, the presence of a gas stove was not a predictor of current respiratory symptoms. Hay fever was negatively associated with the presence of a gas stove, nonrespiratory illness was positively associated, and no association was found for earache.

The logarithm of pulmonary function was fitted to a multiple linear regression model including sex, sex-specific log of height, age, indicators of parental education, maternal smoking, an indicator for gas stove, and indicators for each city. **Maternal smoking was negatively associated with all measures of lung function except FVC (table 3).** For FVC and

FEV_1, the coefficients were comparable to those reported previously (2). The strongest associations were found for $FEV_{0.75}$ and MMEF, two measures not available in the earlier analysis. Because FVC was positively associated with maternal smoking, the ratios of FEV_1 and MMEF to FVC both had strong negative associations with maternal smoking.

The presence of a gas stove was negatively associated with FVC, FEV_1, and $FEV_{0.75}$. These deficits were not statistically significant, but were comparable to earlier estimates (2). MMEF and the ratio measures were positively associated with gas stove, but the associations were not statistically significant.

The city-specific symptom prevalence and pulmonary function levels, adjusted to the population distribution of the covariates described above, are given in table 4.

Associations with Air Pollutant Concentrations

City-specific annual means of the 24-h average air pollution concentrations were calculated for the 12 months preceding the examination of each child and averaged for each city (table 4). For most pollutants, the annual pollution means were lowest in Portage, Topeka, and Watertown and highest in Kingston, St. Louis, and Steubenville. Ozone concentrations, however, were highest in the communities with low concentrations of other pollutants. Except for ozone, the correlations among pairs of pollution measures varied between 0.53 and 0.98. Ozone concentrations were negatively correlated with all other pollutants, −0.96 with NO_2 and between −0.78 and −0.73 otherwise.

Results from regression of the adjusted logits of symptom frequencies on the air pollutant concentrations, expressed as the relative odds of a positive response in the most- and least-polluted city, are given in table 5. Over the range of TSP concentrations observed (34.1 to 80.0 μg/m³) (table 4), the odds of bronchitis were estimated to increase by a factor of 2.31 with a 95% CI of 0.79 to 6.78, and similar results were obtained for PM_{15} (figure 1), $PM_{2.5}$, and FSO_4, the three other measures of particle mass. The association was statistically significant only for PM_{15}. Smaller and nonsignificant associations with bronchitis rates were found for SO_2 and NO_2. No association was found between ozone concentrations and bronchitis rates. Sex-specific regressions did not indicate any difference in response between the sexes. For example,

TABLE 2

ESTIMATED RELATIVE ODDS (95% CONFIDENCE INTERVAL) OF REPORTED SYMPTOMS VERSUS MATERNAL SMOKING AND GAS STOVES, ADJUSTED FOR SEX, AGE, PARENTAL EDUCATION, AND CITY OF RESIDENCE IN CHILDREN 10 TO 12 YEARS OF AGE, SIX CITIES STUDY, 1980–1981 SCHOOL YEAR

	Mother's Smoking (1 pack/day)	Gas Stoves
Respiratory symptoms		
Bronchitis	1.28 (1.07, 1.53)	1.02 (0.77, 1.35)
Chronic cough	1.18 (0.98, 1.41)	0.88 (0.67, 1.16)
Chest illness	1.17 (1.01, 1.35)	0.97 (0.79, 1.20)
Persistent wheeze	1.20 (1.04, 1.40)	0.89 (0.71, 1.11)
Asthma	1.07 (0.85, 1.34)	0.76 (0.54, 1.05)
Reference symptoms		
Hay fever	0.92 (0.78, 1.08)	0.70 (0.56, 0.87)
Earache	1.21 (1.09, 1.35)	0.95 (0.81, 1.12)
Nonrespiratory illness	1.16 (0.94, 1.42)	1.30 (0.96, 1.76)

TABLE 3

ESTIMATED PERCENT EFFECT (95% CONFIDENCE INTERVAL) OF MATERNAL SMOKING AND GAS STOVES ON PULMONARY FUNCTION ADJUSTED FOR SEX, SEX-SPECIFIC LOGARITHM OF HEIGHT, AGE, PARENTAL EDUCATION, AND CITY OF RESIDENCE IN CHILDREN 10 TO 12 YEARS OF AGE, SIX CITIES STUDY, 1980–1981 SCHOOL YEAR

	Mother's Smoking (1 pack/day)	Gas Stoves
FVC	+0.6% (+0.1, +1.1)	−0.5% (−1.2, +0.2)
FEV_1	−0.4% (−0.9, +0.2)	−0.3% (−1.1, +0.5)
$FEV_{0.75}$	−0.7% (−1.3, −0.2)	−0.2% (−1.0, +0.6)
MMEF	−3.4% (−4.5, −2.4)	+1.0% (−0.5, +2.6)
FEV_1/FVC	−1.0% (−1.3, −0.7)	+0.3% (−0.2, +0.7)
MMEF/FVC	−3.9% (−4.9, −2.9)	+1.5% (+0.0, +3.0)

TABLE 4

CITY-SPECIFIC RATES OF SYMPTOMS, PULMONARY FUNCTION, AND 12-MONTH MEAN POLLUTION CONCENTRATIONS FOR CHILDREN 10 TO 12 YEARS OF AGE, SIX CITIES STUDY, 1980–1981 SCHOOL YEAR

	Portage	Topeka	Watertown	Kingston	St. Louis	Steubenville
Respiratory symptoms, %						
Bronchitis	3.6	6.0	4.7	10.0	6.4	8.1
Chronic cough	3.0	7.3	2.3	6.7	6.6	8.7
Chest illness	7.6	11.7	9.3	15.9	7.2	16.1
Persistent wheeze	9.6	11.4	6.6	10.6	8.9	9.6
Asthma	5.1	5.9	3.2	4.4	3.4	3.3
Reference symptoms, %						
Hay fever	20.0	22.7	12.1	23.1	32.8	23.1
Earache	10.7	12.6	10.9	6.7	12.7	5.7
Nonrespiratory illness	4.9	4.3	6.0	5.1	4.5	4.5
Pulmonary function, L						
FVC	2.556	2.492	2.511	2.487	2.511	2.539
FEV_1	2.225	2.142	2.178	2.156	2.166	2.191
$FEV_{0.75}$	2.042	1.960	2.002	1.988	1.983	2.007
MMEF	2.635	2.529	2.585	2.607	2.589	2.611
Pulmonary function ratios						
FEV_1/FVC	0.870	0.859	0.867	0.868	0.862	0.863
MMEF/FVC	1.030	1.014	1.030	1.047	1.031	1.030
Particulate pollution, μg/m³						
TSP	34.1	63.2	53.8	63.8	80.0	71.2
PM_{15}	20.1	33.4	25.8	42.3	37.8	58.8
$PM_{2.5}$	12.7	11.8	17.7	25.7	22.0	36.7
FSO_4	4.3	3.2	5.7	7.9	7.1	13.9
Gaseous pollution, ppb						
SO_2	4.2	3.5	10.5	6.5	13.5	27.8
NO_2	6.5	12.7	19.9	15.4	22.6	22.6
O_3	37.8	30.3	22.0	25.4	23.2	18.0

Definition of abbreviations: TSP = total suspended particles; PM_{15} and $PM_{2.5}$ = particulate matter less than 15 μm and 2.5 μm aerodynamic diameter; FSO_4 = fine-fraction aerosol sulfate

TABLE 5

ESTIMATED RELATIVE ODDS OF SYMPTOMS AND 95% CONFIDENCE INTERVAL BETWEEN THE MOST POLLUTED AND LEAST POLLUTED CITIES FOE EACH POLLUTANT UNIVARIATELY

	TSP	PM_{15}	$PM_{2.5}$	FSO_4	SO_2	NO_2	O_3
Respiratory symptoms							
Bronchitis	2.3	2.5	2.1	2.0	1.5	1.7	0.5
	(0.8, 6.8)	(1.1, 6.1)	(0.8, 5.9)	(0.6, 6.7)	(0.4, 5.8)	(0.5, 5.5)	(0.2, 1.7)
Chronic cough	3.4	3.7	2.3	2.2	1.8	1.6	0.6
	(0.7, 14.5)	(1.0, 13.5)	(0.4, 13.2)	(0.3, 15.2)	(0.3, 12.5)	(0.3, 10.5)	(0.1, 4.5)
Chest illness	1.4	2.3	2.0	1.9	1.5	1.2	0.6
	(0.3, 6.5)	(0.8, 6.7)	(0.6, 6.2)	(0.5, 6.9)	(0.4, 5.9)	(0.3, 4.8)	(0.2, 2.5)
Persistent wheeze	1.1	1.2	1.0	1.0	0.9	0.8	1.2
	(0.5, 2.5)	(0.5, 2.6)	(0.5, 2.2)	(0.4, 2.2)	(0.4, 1.9)	(0.4, 1.6)	(0.6, 2.7)
Asthma	0.7	0.7	0.6	0.6	0.6	0.6	1.9
	(0.3, 1.9)	(0.3, 2.0)	(0.3, 1.4)	(0.3, 1.4)	(0.3, 1.2)	(0.3, 0.9)	(1.0, 3.4)
Reference symptoms							
Hay fever	0.9	0.5	0.4	0.4	0.6	0.8	1.6
	(0.2, 3.8)	(0.2, 1.2)	(0.2, 0.9)	(0.2, 0.9)	(0.2, 1.7)	(0.2, 2.8)	(0.4, 6.0)
Earache	2.1	1.6	1.3	1.3	1.2	1.2	1.0
	(0.6, 7.4)	(0.4, 7.0)	(0.3, 5.6)	(0.3, 6.0)	(0.3, 5.3)	(0.3, 4.9)	(0.2, 4.7)
Nonrespiratory illness	0.9	0.9	1.0	1.0	1.0	1.0	0.9
	(0.5, 1.4)	(0.6, 1.4)	(0.6, 1.6)	(0.6, 1.6)	(0.6, 1.5)	(0.6, 1.6)	(0.6, 1.6)

For definition of abbreviations, see table 4.

the estimated odds for bronchitis versus PM_{15} was 2.48 for boys and 2.60 for girls.

Similar associations were found for chronic cough and chest illnesses. The odds of reported illness were estimated to increase by approximately a factor of two across the range of particulate exposures. Much weaker positive associations were found with SO_2 and NO_2, and a negative association with ozone.

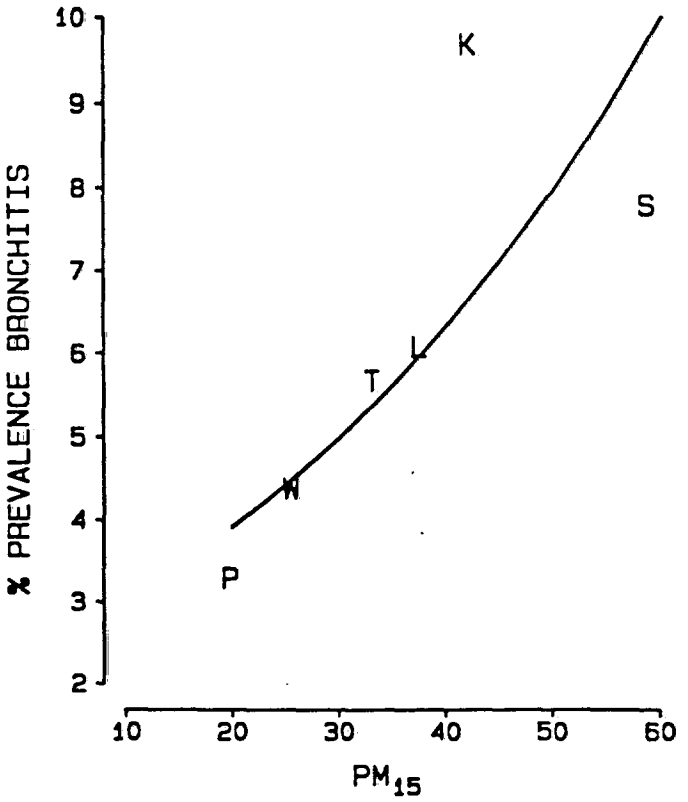

Fig. 1. City-specific prevalence of reported bronchitis versus annual mean PM_{15} concentrations ($\mu g/m^3$) and logistic fit to data (P = Portage, T = Topeka, W = Watertown, K = Kingston, L = St. Louis, and S = Steubenville).

Persistent wheeze was not associated with any of the air pollution measures. Asthma rates were negatively associated with all pollutants except ozone. A similar pattern was found for hay fever, suggesting a higher reporting among those children in the more rural communities. Asthma and hay fever rates were positively associated with annual mean ozone concentrations—estimated relative odds for asthma, 1.88 (95% CI, 1.03 to 3.43) and for hay fever, 1.62 (95% CI, 0.44 to 6.0). Of the other two reference symptoms considered, earache had a weak positive association with the particulate measures, and nonrespiratory illness had estimated relative odds very close to one for each pollutant.

Only TSP concentration was consistently associated with estimated lower levels of pulmonary function. Over the range of concentrations observed, the largest deficit, −2.7% (95% CI, −6.5 to +1.2%), was found for $FEV_{0.75}$. There was little evidence for an association between lower pulmonary function level and the annual mean concentration of any other pollutant.

Susceptible Populations

The prevalence of respiratory symptoms was much higher among the 571 children with asthma or persistent wheeze than among children without these symptoms. Bronchitis was reported among 25.5% of the children with asthma or wheeze versus 4.0% among those without; for chronic cough the rates were 29.5% versus 3.2%, and for chest illness 36.5% versus 7.6%. Although FVC was only 0.3% lower among these children with asthma

TABLE 6

ESTIMATED RELATIVE ODDS OF RESPIRATORY SYMPTOMS AND 95% CONFIDENCE INTERVAL BETWEEN THE MOST POLLUTED AND LEAST POLLUTED CITY FOR EACH POLLUTANT UNIVARIATELY, STRATIFIED BY REPORTED ASTHMA OR PERSISTENT WHEEZE

	Wheeze or Asthma	TSP	PM_{15}	$PM_{2.5}$	FSO_4	SO_2
Bronchitis	No	2.0 (0.9, 4.7)	2.2 (1.1, 4.2)	1.8 (0.8, 4.3)	1.7 (0.6, 4.7)	1.5 (0.5, 4.3)
	Yes	3.2 (0.6, 18.1)	3.8 (0.9, 15.5)	3.5 (0.9, 13.2)	3.1 (0.6, 16.8)	2.0 (0.3, 14.3)
Chronic cough	No	4.1 (1.6, 10.3)	4.1 (1.9, 9.2)	3.0 (0.9, 10.7)	2.9 (0.6, 13.1)	2.4 (0.5, 11.7)
	Yes	4.0 (0.2, 78.2)	5.0 (0.4, 71.6)	2.4 (0.1, 49.5)	2.4 (0.1, 60.6)	1.9 (0.1, 44.1)
Chest illness	No	1.2 (0.3, 5.4)	2.1 (0.7, 6.4)	1.9 (0.6, 5.7)	1.9 (0.6, 6.4)	1.5 (0.4, 5.6)
	Yes	2.3 (0.3, 16.7)	3.8 (1.1, 13.5)	3.1 (0.7, 12.8)	2.9 (0.5, 15.6)	1.9 (0.3, 13.0)

For definition of abbreviations, see table 4

or wheeze, FEV_1 was 4.5% lower, $FEV_{0.75}$ was 4.3% lower, and MMEF was 10.6% lower. These children were considered as a potentially susceptible subgroup, and the associations between air pollutant concentrations and adjusted city-specific respiratory symptom rates and pulmonary function levels for children with and without these symptoms were compared.

The estimated relative odds over the range of each of the particulate measures and SO_2 is given separately for the two groups in table 6. Bronchitis rates gave relative odds of 2.2 (95% CI, 1.1 to 4.2) versus PM_{15} for children without asthma or wheeze. The estimated relative odds were higher, 3.8 (95% CI, 0.9 to 15.5), for those reporting asthma or wheeze. Children reporting asthma or wheeze not only had a higher prevalence of bronchitis, but apparently a stronger association with PM_{15} concentrations (relative odds ratio, 3.8/2.2 = 1.7; 95% CI, 0.5 to 6.3). Although this difference is not statistically significant on the logistic scale, when these results are plotted on a linear prevalence scale (figure 2), it is clear that children with asthma or wheeze were reporting most of the excess number of cases of bronchitis in the more polluted communities. Similar associations were found between bronchitis and each of the other particulate measures. The associations of bronchitis with SO_2 were smaller in magnitude than with the particulate measures, but were larger for children with asthma or wheeze than for those without (table 6). Results for chest illness in the past year were comparable to those for bronchitis, except that the SO_2 association was smaller among children with asthma or wheeze. The association between pollutant concentration and chronic cough was not stronger, however, among those with asthma or wheeze (table 6).

Separate regressions of the adjusted city-specific pulmonary function levels on air pollution for children with and without asthma or wheeze did not show any associations (figure 3).

Discussion

The first aim of these analyses was to re-examine the previously reported associations between air pollution concentrations and respiratory illness and symptom rates in the same children an average of 3 yr older, using exposure data of documented quality obtained under a standardized protocol. These reanalyses showed associations of particulate and sulfur oxide concentrations with respiratory illness and symptom rates that correspond closely to those found in the earlier analyses. Thus, these findings cannot be attributed to errors in the measurement of ambient air pollution concentrations.

In the earlier analyses (1), annual mean TSP concentrations varied between 39.3 $\mu g/m^3$ in Portage and 114.1 $\mu g/m^3$ in Steubenville. This range was associated

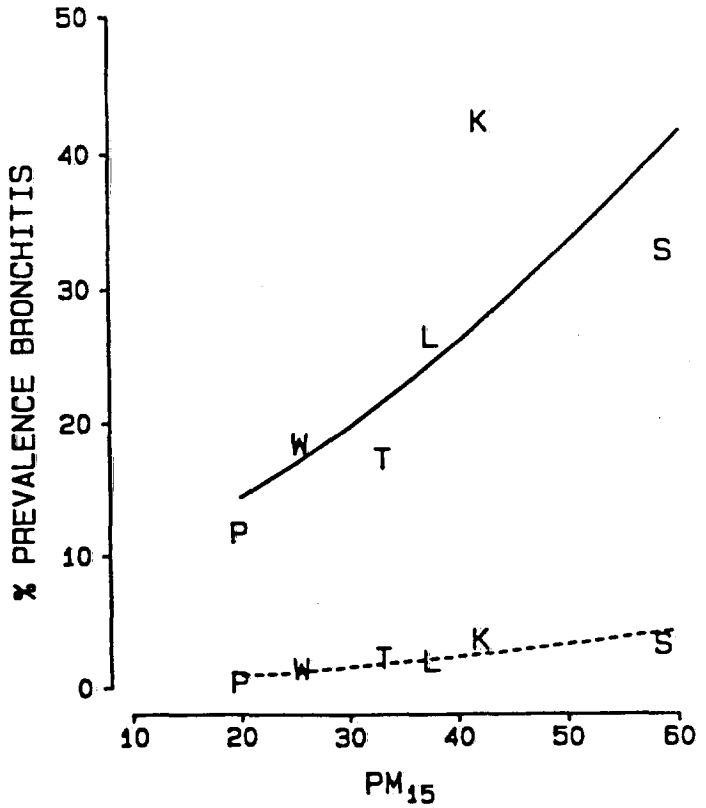

Fig. 2. City-specific prevalence of reported bronchitis versus annual mean PM_{15} concentrations ($\mu g/m^3$) stratified by reported asthma or persistent wheeze. Upper curve (*solid line*) is the logistic fit for children with reported asthma or wheeze, and lower curve (*dashed line*) is the logistic fit for those without (see figure 1 for city labels)

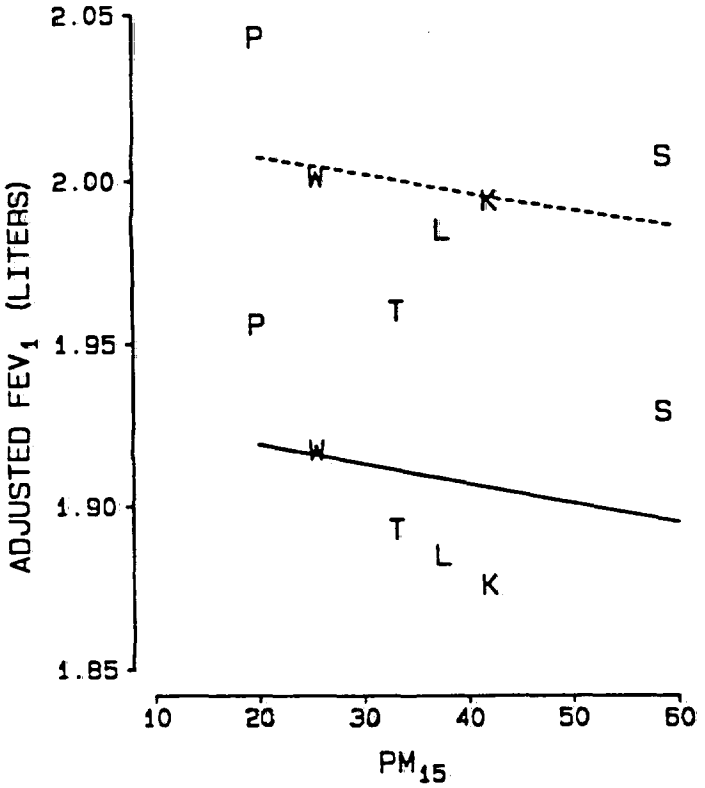

Fig. 3. City-specific adjusted FEV, versus annual mean PM_{15} concentrations ($\mu g/m^3$) stratified by reported asthma or persistent wheeze. Lower curve (*solid line*) is the linear fit for children with reported asthma or wheeze, and upper curve (*dashed line*) is for those without (see figure 1 for city labels).

with a between-cities relative odds for chronic cough of 2.13 with a 95% CI of 1.63 to 2.77. Similarly, the relative odds were 2.13 (95% CI, 1.08 to 4.18) for bronchitis, 1.34 (95% CI, 0.70 to 2.55) for chest illness, and 1.23 (95% CI, 0.76 to 7.00) for persistent wheeze. Despite a decline in the TSP concentrations in the most polluted cities, Steubenville and St. Louis, between the first two examinations in the 1975 to 1977 school years and the 1980–1981 school year, the estimated relative odds obtained in the current analysis are comparable to those obtained earlier. The estimated relative odds for the referent symptoms of hay fever and nonrespiratory illness were not elevated. A positive association was found between earache and particulate pollution, although the association was far from statistical significance. This is consistent with the increased prevalence of earache associated with maternal smoking (table 2).

The differences in respiratory illness reporting between cities may represent differences in the samples of children that are unrelated to air pollution exposure. Those cities visited in the spring have been noted to have both higher rates of respiratory symptom reporting and higher air pollution values. Hence, the positive associations may be attributable in part to better recall of symptoms in the previous winter when questionnaires were administered in the spring compared with those administered in the fall. When season of examination was included in the regression analyses, the estimated relative odds of symptom reporting were reduced. For example, the estimated effect of PM_{15} on reported bronchitis was reduced from 2.52 (table 5) to 1.97 when adjusted for season. Other potential confounders include differences in interpretation of the questionnaire by the respondent and persistent differences in illness or reporting rates associated with ethnic or cultural factors.

The city-specific symptom reporting rates and adjusted level of pulmonary function have been shown to be consistent within each city year to year (1). However, the variability of these summary measures between cities was larger then the random fluctuation between individuals would predict. Because of this clustering effect in the data, two-step methods were used to analyze the health outcomes. The effect of these methods is to produce conservative estimates of the statistical significance of the reported associations compared with commonly used methods. For example, if bronchitis were regressed on PM_{15} exposure for each child, adjusting for covariates in a logistic model, a highly significant positive association is found ($p = 0.000024$). Using the two-step method, bronchitis had a marginally significant positive association with PM_{15} ($p = 0.016$). The estimated odds ratios are similar in both cases. The confidence intervals presented here reflect this adjustment for the clustering of response within city.

In the previous report, data from 3 yr were considered in each city, and three of the cities (Kingston-Harriman, St. Louis, and Steubenville) were divided into two exposure regions based on topography, local sources of pollutants, and air pollution measurements from multiple monitors. This permitted evaluation of the covariance of health status and air pollution within cities. By 1980, there was no evidence for spatial differences in exposure within Kingston-Harriman or St. Louis. The air monitor in Steubenville was located centrally, at a location intermediate between the two previously defined air pollution regions. Thus, the data from the 1980–1981 school year did not allow investigation of the spatial or temporal covariation of air pollution and respiratory health within cities.

The second aim was to investigate the effects of pollutants other than TSP, SO_2, and SO_4, particularly measures of fine particulate air pollution. Because data were available for only six cities, however, the information differentiating pollutants is somewhat limited. Each pollutant was therefore considered univariately, and multivariate comparisons were not attempted.

All of the particulate measures, TSP, PM_{15}, $PM_{2.5}$, and FSO_4, are highly correlated across the six cities. All are associated with substantial increases in the reported rates of respiratory illnesses over the range of annual means observed. Each of these particulate measures has well-known limitations (12, 13). TSP has a poorly defined upper size cut that depends on wind speed and direction. PM_{15} may underestimate exposure because of coarse particle loss in shipping (14). $PM_{2.5}$ is lightly contaminated by less than absolute separation of particles at 2.5 μm.

The FSO_4 concentration may overestimate sulfur concentrations slightly because of conversion of SO_2 to SO_4 on the filter and the assumption that all sulfur is SO_4.

Of the particulate measurements, only associations with PM_{15} were statistically significant. Dzubay and Barbour (14) have reported a loss of between 19 and 53% of coarse particle mass from filters during shipping between the sample site and the laboratory. The potential variable loss of coarse particles in shipping and handling would normally cause concern about the validity of the associations with PM_{15}. However, starting late in 1980, independent measurements of PM_{15} were made by high-volume samplers with sampling heads that removed particles with an aerodynamic diameter greater than 15 μm. The annual mean concentrations for 1981 from these samplers were 22.8 μg/m³ in Portage, 37.6 μg/m³ in Topeka, 29.8 μg/m³ in Watertown, 41.5 μg/m³ in Kingston, 44.3 μg/m³ in St. Louis, and 62.6 μg/m³ in Steubenville. Comparison with PM_{15} concentrations (table 4) shows that the inhalable particulates were higher by an average of 3.4 μg/m³ and the correlation between the annual means was 0.98. Thus, any bias in the PM_{15} caused by shipping losses in these samples must be small. Moreover, such randomly variable error in the exposure measurement would only underestimate the true association.

Bronchitis and chest illness rates were noted to be higher in Kingston than in any of the other cities, including Steubenville, which has the highest particulate pollution concentrations. Lippmann (15) has suggested that these higher respiratory illness rates may be due to the acidity of the suspended particles in Kingston and Steubenville. Acidity measurements were not made in 1980 or 1981, but recent measurements have shown that aerosol acidity is in fact higher in Kingston and Steubenville (16).

Sulfur dioxide, which is also correlated with the particulate measures, has a much weaker association with the respiratory symptoms than the particulate measures. Similar results were found in the earlier study. Nitrogen dioxide annual means are higher in the more urbanized cities (Watertown and St. Louis) and the industrial city (Steubenville) than in the more rural cities (Portage, Topeka, and Kingston). The association of NO_2 with respiratory symptoms, however, was weak.

Ozone concentrations were highest in the most rural community (Portage). Ozone is a secondary pollutant formed by photochemical reactions as polluted air masses move away from the pollution source regions. Primary pollutants such as nitric oxide (NO) rapidly scavenge O_3, converting it to molecular oxygen and the NO to NO_2. Thus, ozone levels tend to be low in regions that are sources of these primary pollutants such as Steubenville, St. Louis, and Watertown and high in more pristine areas such as Portage, Topeka, and Kingston. Negative associations of respiratory symptoms with ozone probably do not represent a protective effect of ozone, but rather indicate the negative correlation between ozone and other pollutants.

The third aim was to test for associations between air pollution and tests of pulmonary function potentially more sensitive than the previously reported FVC and FEV_1. Although $FEV_{0.75}$ and MMEF were more strongly associated with maternal smoking than were FVC or FEV_1, there was still no indication of chronic effects of air pollution on any measure. Lippmann and Lioy (12) has suggested that these chronic effects may be masked by acute changes in pulmonary function associated with exposure on the days or hours immediately before the examination. The annual pulmonary function data are being analyzed to evaluate such acute effects, and will be reported separately.

The analyses were repeated with stratification on reported asthma or persistent wheeze. Although children with reported asthma or persistent wheeze made up only about 10% of the sample, they accounted for approximately half of the children reporting chronic respiratory symptoms. Thus, stratifying by reported asthma or wheeze removes a substantial source of variability in illness and symptom responses. The separate regressions permit comparisons of the air pollution associations in the two groups of children. Positive associations were found between bronchitis, chronic cough, and chest illness and the particulate measures for both groups. The estimated relative odds of bronchitis and chest illness for the particulate measures was approximately twice as large for those with asthma or wheeze, although these differences were not statistically significant. In absolute terms, the adjusted bronchitis rate for children without asthma or wheeze increased from 2.4% in Portage to 5.2% in Steubenville, a rate difference of 2.8% (see figure 2). For children with asthma or wheeze, the adjusted bronchitis rate increased from 13.7% in Portage to 34.7% in Steubenville, a rate difference of 21.0%. Thus, the smaller group of children that reported asthma or wheeze contributes to most of the cases of bronchitis that could be attributed to air pollution.

In summary, these analyses provide further evidence that there is an increase in respiratory symptom reporting across the six cities that is associated with annual mean particulate levels in these communities. Stronger associations were found with concentrations of inhalable particles, PM_{15}, although the power to differentiate the effects of specific size ranges was weak. Unexplained differences in symptom reporting between cities may be explained by specific components of the particle exposure not considered, e.g., aerosol acidity. Such associations are being investigated in later follow-up examinations of these and other cohorts of children.

Children with reported persistent wheeze or asthma were found to have substantially higher reporting rates for respiratory illnesses and lower pulmonary functions. The proportion of these children within the sample varies between communities. In the more polluted communities, a large fraction of these children are reporting respiratory symptoms. Thus, these children appear to be reacting more in response to air pollution exposure than the rest of the sample. Controlled exposure studies of adolescent asthmatics (17) have suggested that such children may be especially responsive.

There was no evidence for an effect of pollution exposure on level of pulmonary function, either in the complete cohort or in the children with reported persistent wheeze. Thus, air pollution exposure may increase respiratory symptom rates without causing irreversible pulmonary function losses. Nevertheless, although respiratory symptoms may be transient, they clearly have health consequences of some importance. **In particular, respiratory illness in childhood has been reported as a risk factor for the subsequent development of respiratory diseases in adulthood and also a risk factor for the development of COPD in smokers** (18). Longitudinal analysis of data provided by these children as they pass through adolescence may provide additional information about the long-term effects of these pollutant exposures.

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